

Award Number: W81XWH-12-2-0129

TITLE: Regional Anesthesia and Valproate Sodium for the Prevention  
of Chronic Postamputation Pain

PRINCIPAL INVESTIGATOR: Thomas E Buchheit MD

CONTRACTING ORGANIZATION: Duke University  
Durham NC 27705-4677

REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

X Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188		
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) October 2015		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 30 Sep 2014 - 29 Sep 2015	
4. TITLE AND SUBTITLE  Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Postamputation Pain			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W81XWH-12-2-0129		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S)  Thomas Buchheit MD			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  Duke University 2200 W Main St Ste 710 Durham, NC 27705			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)  U.S. Army Medical Research and Materiel Command Fort Detrick, MD 21702-5012			10. SPONSOR/MONITOR'S ACRONYM(S)		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT  The purpose of this research is to determine if FDA approved Valproic Acid, commonly used for migraine headache prophylaxis, will also be effective in the prevention of chronic neuropathic pain. Additionally, this research will define the effect of pre-surgical methylation on the susceptibility to chronic pain, the effect of surgically induced methylation changes on the incidence of chronic pain, and the effect of valproic acid on DNA methylation status.  Because this is a double-blinded, randomized controlled trial, we do not anticipate any major findings until the study is closed and the blinding removed. We are pleased to report that there have been no SAEs attributed to study drug, and that the study drug appears to be well tolerated at all three enrollment sites (Walter Reed National Military Medical Center, Duke, and the Durham VA Medical Center) especially at the Durham VAMC in a generally older, debilitated population.					
15. SUBJECT TERMS Amputation, Postamputation pain, Post-surgical pain, Neuralgia, Epigenetics, Valproic Acid, DNA Methylation, Neuropathic pain					
16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT  UU	18. NUMBER OF PAGES  30	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

## Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Overall Project Summary.....	4 – 8
4. Key Research Accomplishments.....	8
5. Conclusion.....	8
6. Publications, Abstracts and Presentations.....	8
7. Inventions, Patents and Licenses.....	8
8. Reportable Outcomes.....	8
9. Other Achievements.....	8
10. References.....	8
11. Appendices.....	8 – 30

## INTRODUCTION

Chronic pain is a significant problem in patients undergoing surgery following military trauma and chronic vascular disease. Symptoms are typically treated with medications such as narcotics, anti-inflammatory drugs, and local anesthetics. Despite these therapies, more than 60% of patients who have an amputation or significant limb injury experience long-term chronic pain. Chronic pain in military personnel and veterans may impair their ability to ambulate or wear a prosthetic device, and may ultimately require the use of chronic narcotic medications. Although sometimes effective for pain, chronic narcotic medications also carry risks of sedation, confusion, and possible addiction. Identifying preventive mechanisms that can be employed at the time of surgery is of utmost importance for military and veteran health systems. Valproates such as valproic acid have a unique advantage over other classes of medicines used for neuropathic pain, as this drug actually modifies the epigenetic mechanisms, such as DNA methylation, and therefore may demonstrate efficacy in preventing the transition from acute to chronic pain. In this study, we will additionally define the gene expression changes that occur in the transition from acute to chronic pain, and any effect that valproic acid may have on these genes.

In summary, this research will investigate the effectiveness of valproic acid vs placebo when added to regional anesthesia in the prevention chronic pain after amputation, stump revision, or surgery for mangled limb with neurologic damage. It will also define the gene expression changes that occur after surgery and the ability of valproic acid to prevent the epigenetic changes that lead to the development of chronic pain.

## KEYWORDS

Amputation, Post-amputation pain, Post-surgical pain, Neuralgia, Epigenetics, Valproic Acid, DNA Methylation, Neuropathic pain

## OVERALL PROJECT SUMMARY

We received all approvals necessary to begin enrollment at the Durham VAMC on 22Nov13. As our first year of enrollment (Grant Year 2) saw fewer numbers of eligible subjects, we requested that Duke University Medical Center be added as a third enrollment site. We received approval for enrollment at DUMC on 19May14, from HRPO on 30Jul14, and from DOD on 02 Oct14. With this third study site, we were able to increase enrollment, although still experienced multiple potential study patients excluded by overly rigid inclusion criteria in regards to renal disease (the study drug is hepatically metabolized).

After meetings with the investigational pharmacist and a thorough review of the literature, we removed renal failure from the list of exclusion criteria at Duke University Medical Center on 24 Jun15. An amendment for the same could not be submitted to the Durham VAMC until after approval of the annual continuing review which was granted on 17 September 2015. In conjunction with new IRB procedures required of investigators, this amendment is presently being prepared for submission by mid-November. This change of inclusion criteria is consistent with the pragmatic “real world” nature of this trial since one of the significant target audiences (chronically ill veterans with vascular disease and diabetes) experiences a high incidence of renal failure. Since the study medication is continued in the treatment of veterans and patients with neuropathic pain, chronic headaches, and bipolar disorder, we believed it appropriate to modify the inclusion/exclusion criteria to mirror standard clinical practice for the treatment of similar conditions. With these protocol modifications, we have continued to increase enrollment. Our last month saw the highest enrollment to date at 5 patients between both the Duke UMC and the Durham VAMC, and it appears to be continually climbing as surgical referral patterns solidify.

During year 3 of this research project, we also analyzed our initial VIPER study data, revealing a 65% baseline incidence of chronic post-amputation pain, higher than anticipated at the start of this Valproate grant. The principle investigator has also participated in a series of discussions with other investigators, including those in the IMMPACT Study Group regarding “meaningful” improvements needed to define significance in the setting of a clinical trial. The conclusions of these discussions are also supported by research literature with guidelines now recommending clinical significance to be defined as between 20-30% improvement<sup>1</sup>. We are currently taking these new data (confirmed baseline incidence of chronic post-amputation pain and percent improvement required for significance) into consideration. With a baseline incidence of 65% chronic pain and a 20% threshold for clinically

significant improvement, 192 total enrolled patients would be required to maintain 80% power for clinical outcomes analysis.

Below is a detailed list of events and accomplishments during Year 3 of this project.

## **Durham VAMC**

### **2014**

NOVEMBER Continuing Review Approval received from DVAMC IRB

### **2015**

MARCH Lori Walther, Human Subjects Protection Scientist, requested a consent form revision. The consent form version 23 October 2013 presented lacked the required DoD language regarding page 11 "Will Anyone Else Have Access to My Research Data?" Documents were submitted to Durham VAMC IRB on 04/16/2016 and approved on 06/16/2015.

APRIL Consent form revision submitted to Durham VAMC IRB on 04/16/2015

JUNE Cosent form revision approved on 06/16/2015

JULY Received Continuing Review Acceptance from Kimberly Odam, Human Subjects Protection Scientist, HRPO

SEPTEMBER Received approval of the annual Continuing Review from the Durham VAMC on 17 September 2015 with approval through 9 September 2016.

OCTOBER Submitted Continuing Review approvals to Lori Walther, Human Subjects Protection Scientist. Additionally, an amendment is being prepared for submission to the IRB to relax exclusion criteria to include patients with End Stage Renal Disease.

A total of 47 patients were screened this quarter, 3 of which were consented and 1 was withdrawn. Of the scheduled follow-ups this quarter, two one-month follow-ups were completed, one three-month follow-up was completed, and one six-month follow-up was completed. A total of 277 patients were screened for the year of which 6 were consented.

## **Duke University Medical Center**

### **2014**

OCTOBER Mrs. Lisa L. Wells Roark (DoD contract specialist) notified the study team of approval of the Scope of work as well as the Re-budget submitted on 06/30/2015

DECEMBER The Continuing Review (CR) Submission Form along with the required supporting documents (USAMRMC Human Research Protection Office CR Checklist, CR Progress Report, Research Summary, CR Summary Report, DOD Checklist, Local IRB approval letter, Quarterly report, Draft ICF, Current copy of protocol and current consent form) were submitted to HRPO for the study at Duke.

### **2015**

APRIL Received Continuing Review Acceptance from Sharon Evans, Deputy Director, HRPO

MAY Protocol amendment to open the study for enrollment in patients with renal disease to avoid unnecessary patient exclusions was submitted.

JUNE IRB approval was received for enrollment of patients with renal disease on 06/24/2015

AUGUST Continuing Review documents submitted to Duke IRB and approved 08/25/2015 with an expiration date of 08/28/2016

SEPTEMBER Amendment submitted to request approval of a phone script for the purposes of conducting pre-screening procedures and obtaining a verbal consent to participate, especially for patients who are admitted over weekends and are first-scheduled surgical cases. Approved on 09/08/2015

A total of 39 patients were screened this quarter, 2 of which were consented. Of the scheduled follow-ups this quarter, two one-month follow-ups were completed, two three-month follow-ups were completed, and three six-month follow-ups were completed. A total of 176 patients were screened for the year of which 9 were consented and enrolled. Of the 9 consented and enrolled, 2 patients were withdrawn (1 expired from causes unrelated to the study), and 1 patient was lost to follow-up.

## **Walter Reed National Military Medical Center**

### **2014**

NOVEMBER The annual continuing review was approved by the WRNMMC IRB. A new stamped consent was received granting approval thru 12/2015.

### **2015**

FEBRUARY WRNMMC\_IRB approved the amendment naming a new Principal Investigator. Our new Principal Investigator is LCDR Michael Kent, MD, USN, MC. Dr Kent is an attending anesthesiologist at WRNMMC. COL Buckenmaier retired from the US ARMY.

APRIL Five patients' complete collection of blood samples was shipped to the Duke University Van de Ven lab for analysis.

SEPTEMBER Four patients' complete collection of blood samples was shipped to the Duke University Van de Ven lab for analysis

A teleconference was held with Mary McDuffie, Veda Byrd, Dr John Hsia, and Dr Thomas Buchheit. New data collection points and protocol language were discussed.

Total follow ups for the year: 22 one month follow ups were done, 16 three month follow ups were done, and 12 six month follow ups.

## **Important Dates of Multi-Site Study Coordination**

### **2014**

DECEMBER S. Becky Perfect and Meghan Jones were added to staff listing at the DVAMC.

### **2015**

JANUARY Clinical phenotype adjudication performed on initial patients reaching 3 month follow-up period

MARCH Veotria (Veda) Byrd was added to the staff listing at the DVAMC.

Meeting held with COL Buckenmaier, Peter Bedocs, Kelly Kiser, Dr. Thomas Buchheit, Dr. Thomas Van de Ven, Alex Chamessian, Dr. John Hsia, Mary McDuffie, Dr. Michael Kent, Nancy Kwon, Rachel Morales, and Veotria Byrd in attendance. Dr. Kent was formally introduced to the whole team. Future goals, expected adverse events, deviations, and case report forms were discussed.

APRIL WRNMMC shipped 5 complete blood sample kits to Duke. Each Sample includes 3 different time collection points. The samples were logged in our database and are being stored at GSRBI.

SEPTEMBER WRNMMC shipped four patients' complete collection of blood samples to Duke. The samples were logged in our database and are being stored at GSRBI.

OCTOBER      Adjudication meetings held on October 9<sup>th</sup> and 27<sup>th</sup> for patients meeting 3 month end point analysis.  
The number of patients with 3 month data was 36 total.

- The chart below summarizes enrollment at Durham VAMC, Duke University Medical Center and Walter Reed.

Project Start Date	09/30/2012	
	# Screened	#Enrolled
<b>DVAMC</b>		
<i>All approvals received 11/22/2013</i>		
Year 3, Quarter 1	28	4
Year 3, Quarter 2	101	0
Year 3, Quarter 3	100	1
Year 3, Quarter 4	47	3
<b>DUMC</b>		
<i>All approvals received 08/25/2014</i>		
Year 3, Quarter 1	47	3
Year 3, Quarter 2	39	3
Year 3, Quarter 3	58	3
Year 3, Quarter 4	39	2
<b>WRNMMC</b>		
<i>All approvals received 03/11/2014</i>		
Year 3, Quarter 1	19	6
Year 3, Quarter 2	20	7
Year 3, Quarter 3	21	4
Year 3, Quarter 4	19	6
<b>Total</b>	<b>538</b>	<b>42</b>

With the change in both exclusion criteria at Duke (06/24/2015) and VAMC (anticipated approval of 11/2015) and the new screening process by the CRC, we now anticipate significant improvements in enrollment for Year 4 of this research.

The SOW dated 23Aug13 is in effect for this year-end report and outlined below.

<b>Task 1 (pre-study) – Human subjects approval (including HRPO)</b>	<b>Months 1-12</b>	<b><i>Actual</i></b>
a. Duration (Durham VAMC), months 1-9		
b. Duration (WRNMMC), months 1-12		
c. Exempt from Review (Duke), months 9-10		
<u>Milestone</u> Pre-Study Task 1a – IRB & HRPO approval in Durham	Month 9	<i>Month 14</i>
<u>Milestone</u> Pre-Study Task 1b – IRB & HRPO approval at WRNMMC	Month 12	<i>Month 17</i>

## Task 2 – Clinical Trial

*Aim1: Determine the efficacy of regional anesthesia and valproate in reducing the incidence of chronic post-amputation pain.*

Patients will be screened at the time of scheduling for surgery. We anticipate screening 19-20 patients per month to enroll approximately 6/month at each site. Subjects will receive either placebo or study drug (valproate) TID for 7 days.

a. Subject enrollment at DVAMC (210 pts)	Months 9-42	
b. Subject enrollment at WRNMMC (210 pts)	Months 12-42	
<u>Milestone</u> Task 2a – First patient enrolled in Durham	Months 9-10	<i>Month 14</i>
<u>Milestone</u> Task 2b – First patient enrolled at WRNMMC	Months 12-13	<i>Month 20</i>
c. First enrolled subjects seen at 3 month endpoint	Months 12-16	<i>Months 15-20</i>

Milestone Task 2c – Endpoint adjudication meetings at 6 & 12 months    Months 18-28  
 d. Review of site enrollment targets

<u>Milestone</u> Task 2d – Enrollment of 140 subjects	Months 24-26	<b><u>Projected</u></b> <i>Months 33-39</i>
e. Interim analysis	Month 30	<i>Month 40</i>
<u>Milestone</u> Task 2e – Endpoint adjudication meetings at 18 & 24 months	Months 30-40	<i>Months 40-46</i>

## KEY RESEARCH ACCOMPLISHMENTS

Our research group has recently published granular phenotypic data from our other VIPER research grant<sup>2</sup>, demononstrating a 65% incidence of chronic post-amputation pain. This is consistent with historical literature, and higher than our original conservative estimate. We have additionally investigated and accessed improved methods of methylation analysis (whole genome bisulfite methylation sequencing) and targeted methyl-DNA immunoprecipitation sequencing as effective laboratory methods. These two advancements will allow improved outcomes for this research grant.

## CONCLUSION

Nothing to report.

## PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

Nothing to report.

## INVENTIONS, PATENTS AND LICENSES

Nothing to report.

## REPORTABLE OUTCOMES

Nothing to report.

## OTHER ACHIEVEMENTS

Nothing to report.

## REFERENCESNA

## APPENDICES

Attachment 1 – Duke University Continuing Review Approval

Attachment 2 – Durham VAMC Continuing Review Approval

Attachment 3 – Year Three Summary Quad Chart

1. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113:9–19.
2. Buchheit T, Van de Ven T, John Hsia H-L, McDuffie M, MacLeod DB, White W, Chameessian A, Keefe FJ, Buckenmaier CT, Shaw AD. Pain Phenotypes and Associated Clinical Risk Factors Following Traumatic Amputation: Results from Veterans Integrated Pain Evaluation Research (VIPER). *Pain medicine* (Malden, Mass.) 2015. Epub. Ahead of Print.



**DukeMedicine**

Institutional Review Board for Clinical Investigations

## IRB NOTIFICATION OF CONTINUING REVIEW APPROVAL

**Continuing Review ID:** CR002\_Pro00047194  
**Principal Investigator:** Thomas Buchheit  
**Protocol Title:** Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain  
**Sponsor/Funding Source(s):** US Department of Defense  
**Federal Funding Agency ID:** W81XWH-12-2-0129  
**Date of Declared Concordance with federally funded grant, if applicable:** N/A

The Duke University Health System Institutional Review Board for Clinical Investigations has conducted the following activity on the study cited above:

<b>Activity:</b>	Continuing Review	<b>Review Type:</b>	Full Committee Review
<b>Review Date:</b>	8/13/2015 IRB 04		
<b>Issue Date:</b>	8/25/2015		
<b>Anniversary Date:</b>	8/28/2015		
<b>Expiration Date:</b>	8/28/2016		

DUHS IRB approval encompasses the following specific components of the study:

<b>Protocol, version/date:</b>	--7/24/2014
<b>Summary, version/date:</b>	--5/18/2015
<b>Consent form reference date:</b>	--8/25/2015 (Duke Consent)
<b>Investigator Brochure, version/date:</b>	--
<b>Pediatric Risk Category:</b>	--

**Other:**

--Forms, VPA Insert, Questionnaire, Phone Scripts (3)  
4/2/2014, Recruitment Material, Waiver.

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.

This study expires at 12 AM on the Expiration Date cited above. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately email Jody Power at [jody.power@duke.edu](mailto:jody.power@duke.edu) or call the IRB Office at 668-5111 and follow the instructions to reach the IRB Chair on call. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the Expiration Date.

No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval for the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five (5) working days of the event.

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514. In addition, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization to the extent required by the U. S. Food and Drug Administration.



DUHS Institutional Review Board  
2424 Erwin Rd | Suite 405 | Durham, NC | 919.668.5111  
Federalwide Assurance No: FWA 00009025

Duke University Health System Institutional Review Board  
**Progress Report and Continuing Review Summary**

Principal Investigator Name: Thomas E. Buchheit, MD

Study Title: "Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain"

IRB #: Pro 00047194

**1. Subject Accrual**

What number of subjects did the IRB approve for you to enroll? 105

Do you wish to request a change in this number at this time? Yes\*            No XX

\*If Yes, you must create and submit an amendment. Otherwise, your enrollment target will not be increased.\*

**2. Please give the following information on your subject enrollment so far:**

	<u>During the Past Year</u>	<u>Cumulative Accrual</u>
a. <b>Number Enrolled:</b> This is the number of subjects who signed a consent form; or who gave verbal consent on a study conducted under a waiver of documentation of consent; OR the number of records reviewed if a retrospective study conducted under a waiver of consent and authorization:	# <u>10</u>	# <u>10</u>
b. Number of potentially vulnerable subjects* enrolled: (*Children; pregnant women; fetuses; neonates (non-viable or of uncertain viability); cognitively impaired adults; adults medically unable to consent; non-English speaking subjects; elderly (>90 years old); employees of Duke University or DUHS; Duke students; educationally/economically disadvantaged; terminally ill (life expectancy <3 months)	# <u>0</u>	# <u>0</u>
c. Number of subjects who read the consent form and/or discussed the study with study staff as part of the consent process but refused to participate:	# <u>14</u>	# <u>14</u>
d. Number of consented subjects who voluntarily withdrew:	# <u>0</u>	# <u>0</u>
e. Number of consented subjects who are lost to contact:	# <u>1</u>	# <u>1</u>
f. Number of consented subjects who were withdrawn by the PI:	# <u>2</u>	# <u>2</u>
g. Number of consented subjects who completed the study: (all interventions and follow-up are complete)	# <u>2</u>	# <u>2</u>
h. Cumulative Accrual (Gender, Ethnicity, and Race):	Complete table below.	

Note: **for retrospective medical record review studies**, the race and ethnicity tables below are not necessary if the answer is "Yes" to the following statement: The medical record reviews in this study included all eligible subjects regardless of their race or ethnicity.

YES            NO

# Duke University Health System Institutional Review Board

## Progress Report and Continuing Review Summary

Total Enrollment Report: Number of Subjects Enrolled to Date (Cumulative) By Ethnicity and Race

Ethnic Category	Females	Males	Unknown or not reported	Total
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	3	7	0	10
Unknown (Individuals not reporting ethnicity)	0	0	0	0
<b>Ethnic Category: Total All Subjects*</b>	<b>3</b>	<b>7</b>	<b>0</b>	<b>10</b>

Racial Categories	Females	Males	Unknown or not reported	Total
American Indian/ Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	2	2	0	4
White	1	5	0	6
More than one race	0	0	0	0
Unknown or not reported	0	0	0	0
<b>Racial Categories: Total of All Subjects*</b>	<b>3</b>	<b>7</b>	<b>0</b>	<b>10</b>

\*The Ethnic Category total must equal the Racial Categories total.

### 3. Study Progress

Please provide a narrative summary of the study progress to date. If your study is closed to enrollment and subjects are in follow-up, please detail your follow-up.

This study is a prospective, randomized double blind phase II trial of VPA for amputation, stump revision surgery or surgery to limb with neurological damage. Patients are randomized on a sequential basis.

Since the last continuing review, 147 patients have been screened, 10 have been consented, and 9 have been enrolled. Five patients are still actively enrolled, 2 patients have completed all study requirements, 2 have been withdrawn by the PI from the study, and 1 patient has been lost to follow-up. It should be stated that low enrollment is attributed to the co-morbid risk factors associated with this population (that is, many are excluded from study participation due to end-stage renal disease, creatinine levels greater than 2.5mg/dL, long-term anticoagulation therapy, seizure disorders requiring anti-epileptic medication, or mental health disorders requiring tricyclic antidepressant therapy greater than 50mg/day).

Additionally, ten amendments have been submitted and approved. Of the ten approved, seven were for personnel changes (additions/removals). The remaining three amendments addressed the following:

**AMD #8** - The maximum number of subjects to be enrolled at Duke

**AMD #10** - Updating the exclusion criteria (i.e., therapy with valproic acid or other valproates, coumadin, chlorpromazine and olanzapine at the time of surgery and study drug administration, BMI > 50, and patients with Chronic Kidney Disease and Creatinine levels greater than 2.5 mg/dL), removing the CBC requirement at 3 months, updating the ICF to include MRN as PHI, noting that de-identified samples will be sent to Quest Diagnostics for Valproate evaluation at the end of study drug administration, and noting that PHI is kept in room 278 of Hanes House (Anesthesiology Research Office) in a locked cabinet

**AMD #17** - Capturing subjects receiving wound vac therapy in REDCap database, removing from exclusion criteria subjects at end-stage renal disease requiring dialysis and with creatinine value of 2.5mg/dL or greater, adding completion of PHQ-2 study questionnaire to 3-month and 6-month follow-up

Duke University Health System Institutional Review Board  
**Progress Report and Continuing Review Summary**

and administration of the DVPRS questionnaire if the patient is not drowsy or sedated during the period of study drug administration.

Finally, there was a period of approximately 3 months where there was not a full-time lead CRC available to actively work the study. A CRC was hired in March 2015 to replace the former CRC who relocated from the area.

**4. Conflict of Interest**

- a. Do any of the participating study investigators or other key personnel (or their immediate family/significant other) have a financial or intellectual interest in, or are receiving compensation from, the sponsor or the drugs, devices or technologies used in this research?

☒ No

☐ Yes. If yes, has this conflict been disclosed to the Duke COI Committee?

☐ No

☐ Yes

- b. Are you or any other key personnel an inventor of any of the drugs, devices or technologies used in this research?

☒ No

☐ Yes. If yes, have you filed an Inventor Disclosure Form?

☐ No

☐ Yes

- c. Do you have or anticipate (within the year) any financial relationships (e.g., consulting, speaking, advisory boards, patents, equity, options) that could be perceived to overlap or present a conflict of interest with the current proposal?

☒ No

☐ Yes. If yes, describe the overlap:

- d. Do you have a conflict of interest management plan (issued by the Duke University School of Medicine Research Integrity Office) with this company?

☐ No

☐ Yes

**5. Please answer the following:**

- a. Has there been or do you anticipate a change in the size, scope or scale of the research in the coming year which will require additional resources?

☒ No

☐ Yes. If yes, please explain:

- b. Please summarize the benefits to subjects as a result of participation in this research.

Research has demonstrated that members of this population group will have a 60-70% probability of experiencing chronic post-amputation pain. The primary focus of the research is to determine if patients who receive the study drug have a reduction in chronic pain. We hope to substantiate the intended finding of this research by increasing the knowledge base surrounding chronic pain in other populations and medical disciplines through both the clinical findings as well as the epigenetic and genomic component of this research. As such, this will be beneficial to all subjects in this research and future patients suffering with chronic pain

Duke University Health System Institutional Review Board  
**Progress Report and Continuing Review Summary**

**c. Since the initial IRB review or last Continuing Review (renewal):**

Have there been any events requiring prompt reporting to the IRB, such as a study-related adverse event of any severity, injury, or protocol deviation/violation, that was both unanticipated and indicated that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized?

☒ No.

☐ Yes. If yes, please summarize the events:

If yes, did you promptly report this to the IRB?

☐ Yes.

☐ No. If no, please promptly report the event(s) to the IRB by submitting a Safety Event in eIRB.

Has there been an unexpected excess of expected adverse events?

☐ Yes. If yes, please explain:

☒ No.

Did adverse events occur at the expected frequency and level of severity as documented in the research protocol, any associated research documents, and the informed consent document?

☒ Yes.

☐ No. If no, please explain:

Has the occurrence of the event(s) changed your current risk-benefit assessment (increased potential for risk or decreased potential for benefit to study participants)?

☒ No. If no, please explain your answer:

The events which occurred are related to the co-morbidities associated with the study population, pharmacology associated with the surgical intervention, and post-operative care. Such events include readmission for wound debridement, difficulty with pain management, and recurrent ulcer formation.

☐ Yes. If yes, how did you respond?

☐ No adverse events have occurred since the last IRB review.

**d. Have there been any **complaints** about the research or other problems since initial IRB review or the last continuing review (renewal)?**

☒ No

☐ Yes. If yes, please describe all complaints or other problems.

Duke University Health System Institutional Review Board  
**Progress Report and Continuing Review Summary**

Was each complaint resolved by the research team?

☐ Yes

☐ No. If no, was the event promptly reported to the IRB?

☐ Yes

☐ No

If no, why not?

e. Do the current subject enrollment demographics differ substantially from the anticipated distribution?

☒ No

☐ Yes. If yes, please explain.

f. If no subjects were enrolled this year, please provide an explanation.

g. Have there been any subject withdrawals (either subject or PI initiated) since initial IRB review or the last continuing review (renewal)?

☐ No

☒ Yes. If yes, please explain the reason for all withdrawals.

There have been two withdrawals since the last continuing review, both PI initiated. One subject was withdrawn due to increased confusion and the other was withdrawn after being treated for a perforated ulcer and being intubated thereby rendering him unable to take the oral study drug.

h. Have any subjects been incarcerated (become prisoners) since initial IRB review or the last continuing review (renewal)?

☒ No

☐ Yes. If yes, please provide further information.

i. **Since initial IRB review or the last continuing review (renewal):**

Has there been any literature or new information that relates to your research, such as information about possible risks to human subjects associated with this research or any significant new findings which may relate to the subjects' willingness to continue participation?

☒ No

☐ Yes. If yes, please explain. (Note: Any significant new findings which may relate to the subjects' willingness to continue participation must be conveyed to the subjects in the consent form.)

j. Have any preliminary results of the research come available since initial IRB review or the last continuing review (renewal)?

☒ No

☐ Yes. If yes, please explain. (Note: Any significant new findings which may relate to the subjects' willingness to continue participation must be conveyed to the subjects in the consent form.)

k. Have any publications been derived from this study?

☒ No

☐ Yes. If yes, please list below or provide as an attachment.

l. Have there been any multi-center trial reports?

10/23/2012

Duke University Health System Institutional Review Board  
**Progress Report and Continuing Review Summary**

- ☐ No  
☐ Yes. If yes, please summarize their findings or provide as an attachment.

- m. Since initial IRB review or last continuing review (renewal), have there been any significant changes to what is generally accepted as standard clinical care for those people from whom the subject population will be drawn?

- ☒ No  
☐ Yes. If yes, please explain.



Date: Friday, September 04, 2015 1:59:48 PM

Print Close

## 01. Progress Report Type

\* Select the type of Progress Report you are creating:  
Type

- ☒ Continuing Review
- ☐ Final Progress Report

## 02. Study Enrollment Status

Indicate the current study enrollment status:

Description

- ☐ Study initiation is pending (not yet open for enrollment of new subjects)
- ☒ Open for enrollment of new subjects
- ☐ Closed to enrollment of new subjects but some enrolled subjects are still receiving study drug or other interventions that are more than minimal risk
- ☐ Closed to enrollment of new subjects; all enrolled subjects have completed the study but some subjects continue for observation or follow up
- ☐ All study enrollment and subject involvement is complete but data analysis is ongoing
- ☐ Ongoing retrospective research with no direct subject contact

## 03. Changes to Study Documents

\*Since the initial IRB review or last Continuing Review (renewal):

Have there been any substantial changes to the study (protocol, consent forms, or other study documents) or to the risk-benefit assessment?

☒ Yes ☐ No

If Yes, summarize the changes here. NOTE: If any of these changes have not yet been submitted to the IRB, these changes must be reported via an Amendment.

Besides the addition of study personnel since the last Continuing Review, AMD #10 was submitted to update exclusion criteria (i.e., therapy with valproic acid or other valproates, coumadin, chlorpromazine and olanzapine at the time of surgery and study drug administration), BMI > 50, and patients with Chronic Kidney Disease and Creatinine levels > 2.5 mg/dL. Additionally, the CBC requirement at 3 months was removed. Also in AMD#10, the ICF was updated to include MRN as PHI and de-identified samples will be sent to Quest Diagnostics for Valproate evaluation at the end of study drug administration. Finally, the location of PHI was established, and the protocol was updated to reflect that the DVPRS questionnaire will be administered if the patient is not drowsy or sedated during the period of study drug administration.

Most recently, AMD #17 was submitted to capture subjects receiving wound vac therapy in REDCap, to remove from the existing exclusion criteria subjects at end-stage renal disease requiring dialysis and with creatinine values of 2.5mg/dL or greater, and to add completion of the PHQ-2 study questionnaire to 3-month and 6-month follow-up visits. (This was done after conferring and confirming with the pharmacist that patients in this sub-population would not be adversely affected if they were to receive the study drug through randomization.)

## 04. Audits

**\*Since the initial IRB review or last Continuing Review (renewal):**

Has one or more internal or external audit reviews been conducted on this study?

☐ Yes ☒ No**If Yes, indicate the auditing entities (eg. FDA, sponsor, Duke CTQA Office) and briefly summarize the audit findings.**

Attach a copy of the audit report(s) or relevant correspondence:

Document Name	Date Created	Last Modified	Revision
There are no items to display			

**05. Interim Reports****\*Since the initial IRB review or last Continuing Review (renewal):**

Have you received an interim report on the study from an external monitoring board such as a data and safety monitoring board (DSMB) or an annual report from a sponsor or cooperative group?

☐ Yes ☒ No**If Yes, Attach a copy of the interim report(s):**

Document Name	Date Created	Last Modified	Revision
There are no items to display			

**06. Funding Source****\* Select one:**

- ☐ Federally funded -- Competing renewal
- ☐ Research is not funded by Federal Government
- ☒ Federally funded -- Non-competing renewal

**If this research is Federally funded, complete the following:**

Attach either the complete grant application for competing renewals, or the grant progress report for non-competing renewals:

Document Name	Date Created	Last Modified	Revision
VPA Year 3, Quarter 3 Report to Sponsor	7/17/2015 1:53 PM	7/17/2015 1:53 PM	0.01

**07. Progress Report**

Enter the date contact with human subjects began (if applicable):

5/19/2014

Attach either Continuing Review Progress Report or Final Progress Report as applicable:

Document Name	Date Created	Last Modified	Revision
CR Progress Report with track changes (8-24-15).doc	7/17/2015 3:47 PM	8/24/2015 10:06 AM	0.02

**End of Continuing Review Form**

You have reached the end of the Continuing Review form. Upon clicking the "Finish" button below, this continuing review **will not** automatically be submitted for review. It will instead appear under the

"Presubmission" tab on your workspace, allowing further edits to be made later if it is not yet ready for submission.

If this continuing review is complete and ready to be submitted for review, you must click the "Submit Continuing Review" activity button, located in the left column of this continuing review's workspace, to begin the Duke HRPP review process.

**Assoc Ch of Staff  
Durham VAMC Research (151)**

508 Fulton St. • Durham, NC 27705 • 919-286-6926 • Fax: 919-286-6824

---

September 23, 2015

Thomas F. Buchheit, MD  
508 Fulton Street  
Durham, NC 27705

Study 01709/001 Regional Anesthesia & Valproate Sodium for Prevention of Chronic Post-Amputation Pain

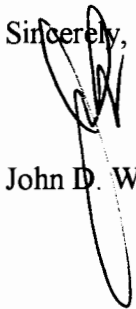
This is a notification to inform you that the required annual review has occurred and this study is approved by all relevant research subcommittees to continue.

You are reminded that no changes or modifications may be implemented for this study, except where necessary to eliminate apparent immediate hazards to subjects, until you have requested and received full approval from all applicable subcommittees.

You are also reminded that all study personnel with a Durham VAMC appointment (e.g., VA-paid, WOC, or IPA) must remain current with all applicable research training and must maintain a current Research Scope of Practice document.

No research may be continued beyond the designated approval period.

Sincerely,



John D. Whited, M.D, M.H.S.

**Institutional Review Board  
Durham VAMC Research (151)**

508 Fulton St. • Durham, NC 27705 • 919-286-6926 • Fax: 919-286-6824

---

**IRB APPROVAL - Continuing Review**

Date: September 17, 2015

From: Sandra Zinn, Ph.D., Chairperson



Investigator: Thomas F. Buchheit, M.D.

Protocol: Regional Anesthesia & Valproate Sodium for Prevention of Chronic Post-Amputation Pain

ID: 01709 Prom#: 0001 Protocol#: N/A

The following items were reviewed and approved at the 09/10/2015 meeting:

- Conflict of Interest (08/21/2015; TB, SP, CS, TV, JH, & JH)
- Project Data Sheet (08/21/2015)
- Pt admitted to Emergency Department for hypotension and disorientation in the setting of poor oral intake and diarrhea. Admitted to MICU for management of his borderline tenuos blood pressures treated [Not related, Severity: Moderate]

AE#: N/A • AE Dt: 02/23/2015 • Report Dt: 03/02/2015

- Pt was admitted to DVAMC for hypotension (hypovolemic/spectiv shock) Transferred to MICU and was found to have AKI leukocytosis, new left pleural effusion, delirium and a new sacral decubitus ulcer... [Not related, Severity: Moderate]

AE#: N/A • AE Dt: 01/16/2015 • Report Dt: 02/02/2015

- amputation, staph aureus & enterbacter, above knee amputation, hypotensice transfered to CCU [Not related, Severity: Serious]

AE#: N/A • AE Dt: 12/26/2014 • Report Dt: 01/14/2015

- Pt hist of anemia, PVD & chronic renal insufficiency. Earlier stent attempt unsuccessful pt underwent a BKA, post-op complicated by C-diff, pt readmitted with UTI, anemia & cellulitis at surgical site [Not related, Severity: Serious]

AE#: N/A • AE Dt: 12/09/2014 • Report Dt: 12/10/2014

- HIPAA Authorization (04/09/2015; received 4/21/2015)
- Memorandum (08/21/2015; From Dr Buchheit)
- Staff Listing (08/21/2015)
- Informed Consent (05/26/2015; Revised Rec'd 05/28/2015 IRB - 5/14/15)
- Request for Continued Approval (08/21/2015)

The following additional items were received to address stipulations and are now approved:

- Conflict of Interest (09/15/2015; KR)
- Response to Recommendations - IRB - 9/10/15 (09/15/2015; Form Dr Buchheit)
- Memorandum - IRB - 9/10/15 (09/15/2015; Form Dr Buchheit)
- Protocol Deviation (09/15/2015; Deviation Log IRB - 9/10/15)

The following Institutional Review Board members recused themselves (or were otherwise excused) from

Page 1 of 2

The Durham VAMC IRB is not connected with, has no authority over, and is not responsible for human research conducted at any other institution, except where a Memorandum of Understanding specifies otherwise. Separate consent forms, initial reviews, continuing reviews, amendments, and reporting of serious adverse events are required if the same study is conducted at multiple institutions.

deliberations and did not vote: Srinivas Pyati, M.D.

**Approval is granted for a period of 12 months and will expire on 09/09/2016. Your Continuing Review is scheduled for 08/11/2016, and the requirements are attached.**

The protocol was determined to have the following level of risk:  
Greater than Minimal Risk

The purpose of this greater than minimal risk multi-site research study is to find out if Valproic Acid (VPA) will prevent chronic nerve pain after amputation or limb injury surgery. Valproic acid is already approved by the U.S. Food and Drug Administration (FDA) in the treatment of headaches and seizure disorders. The use of VPA in this study is investigational because VPA is not specifically approved by the FDA for use in preventing chronic pain after surgery. This continuing review reports that this project is open to prospective recruitment/enrollment, active: participants enrolled and/or randomized and/or undergoing interventions. Since the last report, five participants entered into this study. The Adverse Events that occurred have been submitted. The Conflict of Interests were reviewed and found to be acceptable. The IRB voted to contingently approved the continuation review pending a response to their recommendations. The response to recommendations was received 9/15/15 and final approval was granted 9/17/15.

The following other committee reviews are scheduled:  
Subcommittee on Research Safety (SRS) [08/19/2016]

Approval by each of the following is required prior to study continuation (unless Exempt):  
Institutional Review Board  
Research & Development Committee

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

# Durham VAMC: Request for Continuing Review of Research

IRB  
JRS

Principal Investigator: THOMAS E. BUCHHEIT, MD	MIRB #: 01709
Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain	Date: 08/06/15
[Research Office Use Only] Continuing Review Approved: <u>9/10/15</u> until: <u>9/9/16</u>	

**A. Study Status at the Durham VAMC:** Please choose a response that best describes your study status. If none are applicable, check "other" and explain.

<input type="checkbox"/>	Retrospective chart review or study of existing data/specimens:	
	<input type="checkbox"/> No new charts or specimens being reviewed/analyzed	
	<input type="checkbox"/> Continuing to review charts or specimens	
<input type="checkbox"/>	Prospective recruitment/enrollment has not started	
<input checked="" type="checkbox"/>	Open to prospective recruitment/enrollment:	
	<input checked="" type="checkbox"/> Active: Participants enrolled and/or randomized and/or undergoing interventions	
	<input type="checkbox"/> No participants enrolled and/or randomized	
<input type="checkbox"/>	Closed to prospective enrollment:	Date Enrollment Closed:
	<input type="checkbox"/> Participants undergoing interventions	
	<input type="checkbox"/> Participants in follow-up	
	<input type="checkbox"/> Data analysis only	
<input type="checkbox"/>	Recruitment-only (e.g., study procedures conducted at Duke or UNC, etc.)	
<input type="checkbox"/>	Study completed: Close administrative files	
<input type="checkbox"/>	Other, explain:	

**B. Research Procedures:** Identify applicable experimental procedures in the study.

a.	<input type="checkbox"/> FDA-monitored treatment (IND or device) If yes, provide IND/IDE #:
b.	<input type="checkbox"/> FDA-exempted drug or device (for minimal risk device check "k" below)
c.	<input checked="" type="checkbox"/> Novel combination of FDA-approved drugs or approved drug administered in novel context
d.	<input type="checkbox"/> FDA-approved drug administered in accepted clinical context
e.	<input type="checkbox"/> Surgical procedure (if any surgical component altered for research purposes)
f.	<input checked="" type="checkbox"/> Other invasive procedure (e.g., x-ray, anesthesia or arterial blood draw)
g.	<input checked="" type="checkbox"/> Venous blood draw
h.	<input type="checkbox"/> Benign prospective collection of specimens (through swab, fluid collection, etc.)
i.	<input type="checkbox"/> Behavioral medicine intervention (including exercise, diet, or sleep modification)
j.	<input type="checkbox"/> Experimental behavioral interaction with participant (e.g., psychotherapy)
k.	<input type="checkbox"/> Data from imaging or minimal risk device (if X-ray or radiologic agent used, check 'f' above)
l.	<input checked="" type="checkbox"/> Observation or measurement of behavior (survey, cognitive testing, functional evaluation)
m.	<input type="checkbox"/> No participant interaction; data obtained from existing specimens, recordings or databases
n.	<input checked="" type="checkbox"/> Other: In 'l' above, an abbreviated Mini Mental Health Status Examination is administered prior to consenting a participant to ascertain a level of cognition. Additionally, a PHQ2 (Depression Screening Questionnaire) is administered after Informed consent is obtained along with a number of surveys related to pain and amputation status. During study drug administration, a Richmond Agitation Sedation Scale is used to assess patients during hospitalization.

Final 8/2015

# Durham VAMC: Request for Continuing Review of Research

Investigator: THOMAS E. BUCHHEIT, MD	MIRB: 01709	v.2014-06-12	Page 2 of 8
--------------------------------------	-------------	--------------	-------------

## C. Risks

1. Indicate risk level: ☐ Minimal risk ☒ Greater than minimal risk
2. Are there any special privacy risks? ☐ N/A
- ☒ Genetic analysis ☐ Voice/image recording ☐ Social/financial risk

## D. Participant Information

1. Are non-Veterans enrolled in this study? ☒ Yes ☐ No
2. As applicable, indicate the number of participants and/or records and/or specimens entered for the review period and since the inception of the study. Also provide information on withdrawals during this review period.

Enrollment Type		Prior enrollment	During this review period
<input type="checkbox"/>	Number of <b>participants</b> enrolled:	9	5
	Number of participants withdrawn:	0	0
	<i>Number withdrawn during this review period:</i> a. Lost to follow-up:                      d. Participant died: b. Clinical/Safety reasons:                e. Ineligibility: c. Non-adherence to protocol:            f. Other:		

### For Retrospective Studies:

<input type="checkbox"/>	Number <b>records</b> enrolled:		
<input type="checkbox"/>	Number of records withdrawn:		
	If applicable, reason(s) for withdrawal(s):		

<input type="checkbox"/>	Number <b>specimens</b> enrolled:		
<input type="checkbox"/>	Number of specimens withdrawn:		
	If applicable, reason(s) for withdrawal(s):		

3. Enter the cumulative participant gender and minority status for the Durham site only.
- ☐ The study enrolled human subjects but gender and minority status were not collected.

2a. Race	Females	Males	Sex/Gender unknown or not reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	4	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	0	10	0	10
More than one race	0	0	0	0
Unknown or not reported	0	0	0	0



# Durham VAMC: Request for Continuing Review of Research

Investigator: THOMAS E. BUCHHEIT, MD

MIRB: 01709

v.2014-06-12

Page 3 of 8

## D. Participant Information

### 2b. Ethnicity

Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	0	14	0	0
Unknown or not reported	0	0	0	0

\*The Ethnic Categories total must equal the Racial Categories total.

4. Number of participants considered to be members of specific vulnerable populations:

	Females	Males	Sex/Gender Unknown or not reported	Total
Pregnant women	0	0	0	0
Prisoners	0	0	0	0
Children	0	0	0	0
Subjects who lack decision making capacity	0	0	0	0

5. Do you make a reasonable effort to provide the "Volunteering in Research" brochure in settings where subjects may be recruited (e.g., clinic areas)? ☒ Yes ☐ No ☐ N/A

6. Do you make a reasonable effort to provide the "Volunteering in Research" brochure to each prospective subject when that individual is approached to take part in the study?

☒ Yes ☐ No ☐ N/A

## E. Informed Consent and HIPAA Authorization

1. Does this study have waivers of informed consent and HIPAA authorization to screen and recruit?

Yes No

☒ ☐

2. What type of informed consent was used?

☒ Written consent form

☐ Waiver of documentation of informed consent

☐ None: Waiver of informed consent

3. If applicable, include the currently approved ICF.

☐ Not applicable

4. Were all participants enrolled at Durham entered on a master list of subjects after signing and dating the approved ICF prior to undergoing any study interactions or interventions?

☒ ☐

☐ Not applicable: The IRB granted a waiver of informed consent or a waiver of documentation of informed consent

5. What type of HIPAA authorization was used?

☒ Written HIPAA authorization

# Durham VAMC: Request for Continuing Review of Research

Investigator: THOMAS E. BUCHHEIT, MD

MIRB: 01709

v.2014-06-12

Page 4 of 8

## E. Informed Consent and HIPAA Authorization

Yes

No

☐ None: Waiver of HIPAA authorization

6. If applicable, include the currently approved HIPAA authorization.

☐ Not applicable

## F. Amendments

1. Provide a list of all amendments to the protocol since last IRB initial or continuing review, whichever is most recent. If more space is needed, attach additional page(s) as necessary.

☐ There have been no amendments since the last IRB review.

Amendment Approval Date	Brief Description of Amendment
1/8/15	Added minor protocol changes including the addition of Duke as a recruitment site and written clarification on blood draws.
6/6/15	Added PHQ-2 (questionnaire) to 3mo and 6mo visits, adding several organizations in the ICF and HIPAA Authorization to the list of people who may have access to patient research data (USAMRMC, other government agencies, the Durham VAMC IRB, FDA, Duke University, Metabolon Inc., and Quest Diagnostics), listing specific action to be taken regarding depression and/or abuse in the ICF/protocol, removing personnel, adding details regarding: 1) study blood coding/de-identification, 2) how subjects could be de-coded, and 3) the specific REDCap URL.

## G. Data Safety Monitoring and Risk / Benefit Assessment

Yes

No

N/A

1. Have there been any adverse events (AEs) in this review period?

☒

☐

☐

If yes, attach a summary/list of all AEs that have occurred during the review period. **ATTACHED**

2. Have there been any Serious Adverse Events (SAEs) in this review period?

☒

☐

☐

If yes, attach a summary/list of all AEs that have occurred during the review period. **ATTACHED**

☐ SAEs that did not have to be reported within 5 business days are attached.

☒ All local unanticipated SAEs (whether related or unrelated to the research) that required 5-business day reporting have already been submitted to the IRB.

3. Have there been any unanticipated problems involving risks to subjects or others during the review period?

☐

☒

☐

If yes, attach a summary/list of all unanticipated problems that have occurred during the review period.

☐ Unanticipated problems that did not have to be reported within 5 business days are attached.

# Durham VAMC: Request for Continuing Review of Research

Investigator: THOMAS E. BUCHHEIT, MD	MIRB: 01709	v.2014-06-12	Page 5 of 8
--------------------------------------	-------------	--------------	-------------

G. Data Safety Monitoring and Risk / Benefit Assessment	Yes	No	N/A
<input checked="" type="checkbox"/> All local unanticipated problems that required 5-business day reporting have already been submitted to the IRB.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Have there been any protocol or policy deviations during this review period? <i>If yes, attach a summary/list of all deviations. <b>ATTACHED</b></i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Have there been any summaries, recommendations, or minutes from DMC/DSMB meetings or findings based on information collected by the data and safety monitoring plan? <i>If yes, submit with continuing review package.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6. Have there been any subject claims of injury or complaints regarding the research since the last Continuing Review and/or Initial Review? <i>If yes, describe:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

H. Is this study part of a multi-center research project?	Yes	No
<i>If yes:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
1. Durham is the lead site & other sites' IRB initial approvals were/will be submitted.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
2. If available, relevant multi-center trial report(s) are attached. <input type="checkbox"/> N/A	<input type="checkbox"/>	<input type="checkbox"/>

I. Conflict of Interest	Yes	No
1. I have attached Conflict of Interest statements for all Investigators.	<input checked="" type="checkbox"/>	<input type="checkbox"/>

J. Overview / Findings
<p>This study is a prospective, randomized double blind phase II trial of VPA for amputation, stump revision surgery or surgery to limb with neurological damage. Patients are randomized on a sequential basis.</p> <p>Since the last continuing review, 230 patients have been screened, 4 have been consented and enrolled, and 3 have completed the study (as of 8/5/15). Low enrollment is attributed to the co-morbid risk factors associated with this population (that is, many are excluded from study participation due to end-stage renal disease, creatinine levels greater than 2.5mg/dL, long-term anticoagulation therapy, seizure disorders requiring anti-epileptic medication, or mental health disorders requiring tricyclic antidepressant therapy greater than 50mg/day).</p> <p>Two (2) amendments were submitted and approved for this protocol. The details of the amendments and protocol changes are noted in #F. Additionally, a triennial compliance review was performed (7/8/15), and no deficiencies were noted.</p> <p>Finally, there was a period of approximately 3 months where there was not a full-time lead CRC available to actively work the study. A CRC was hired in March 2015 to replace the former CRC who relocated from the area.</p>

## Durham VAMC: Request for Continuing Review of Research

Investigator: THOMAS E. BUCHHEIT, MD

MIRB: 01709

v.2014-06-12

Page 6 of 8

### J. Overview / Findings

2. If available, provide research findings to date. ☒ N/A

This study is still ongoing. No data analysis has been conducted nor are there research findings.

3. If available, provide new scientific findings in the literature, or other relevant findings, that may impact the research. ☒ N/A

4. Have there been any study publications since the last and/or initial review? ☐ Yes ☒ No  
If yes, attach the publication(s) with this submission.

5. If applicable, was the VA acknowledged in each publication? ☒ N/A ☐ Yes ☐ No

☒ Considering all of the above, the risks in this project are still outweighed by the benefits.

VERIFICATION: I am aware that all research projects using human subjects must receive prior approval by the IRB, that any change in this project requires prior approval by the IRB, that consent must be obtained from each subject before entry into the study unless waived, that continuing review is required at least once annually, that projects using human subjects not receiving favorable review must be discontinued, and that a copy of all consent forms (as applicable) and study-related matters must be retained by the Principal Investigator according to VA policy.

Thomas E. Buchheit, MD

Principal Investigator Signature

Date

### FOR RESEARCH OFFICE USE ONLY:

<input type="checkbox"/> Approve <input checked="" type="checkbox"/> Contingent Approval <input type="checkbox"/> Disapprove <input type="checkbox"/> Table	
Comments:	
IRB Member Signature:	Date: SEP 1 '15 11:06 9/10/15

<input checked="" type="checkbox"/> Approve <input type="checkbox"/> Contingent Approval <input type="checkbox"/> Disapprove <input type="checkbox"/> Table	
Comments:	
SRS Member Signature: ( <input type="checkbox"/> Not Applicable)	Date: 9-18-15

## Durham VAMC: Request for Continuing Review of Research

Investigator: THOMAS E. BUCHHEIT, MD	MIRB: 01709	v.2014-06-12	Page 7 of 8
--------------------------------------	-------------	--------------	-------------

☐ Approve   ☐ Contingent Approval   ☐ Disapprove   ☐ Table

Comments:

R&DC Member Signature:

☒ Not Applicable)

Date:

# Regional Anesthesia & Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Log #PT110575

Award Number W81XWH-12-2-0129



PI: Thomas Buchheit MD

Org: Duke University

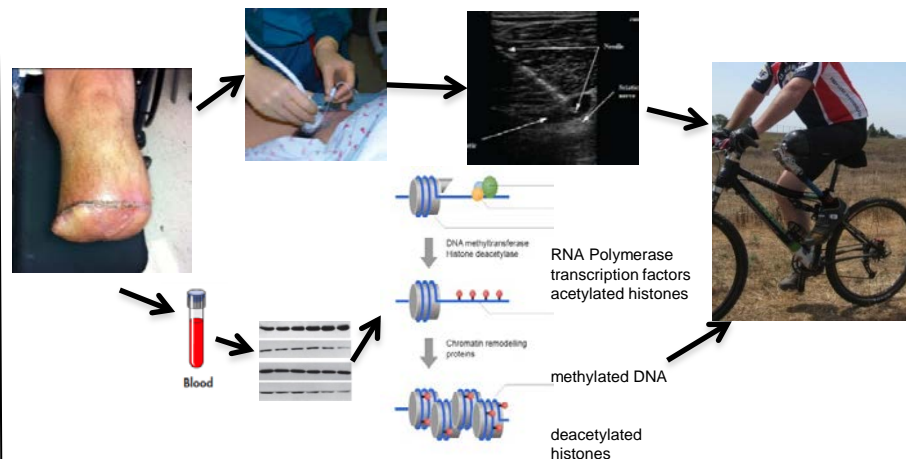
Award Amount: \$2,237,227

## Study/Product Aim(s)

- Aim 1: Determine the efficacy of valproic acid combined with regional anesthesia in reducing the incidence of chronic post-amputation pain.
- Aim 2: Determine role of epigenetic DNA methylation in post-amputation pain and effects of valproic acid treatment

## Approach

- In a randomized clinical trial, we will determine if the combination of valproic acid combined with regional anesthesia reduces the incidence of chronic post-amputation when compared with regional anesthesia alone.
- We will analyze DNA methylation patterns of patients with post-amputation pain and determine the way they are modified by valproic acid. We will confirm the functional relevance of these modifications using gene expression signatures.



Accomplishments: 1. End-point adjudication of initial 36 patients enrolled 2. Increased enrollment with third clinical site 3. Improved laboratory epigenetic and genetic analysis techniques

## Timeline and Cost

Activities	CY	13	14	15	16
VA/Duke/HRPO approvals; Durham VA/Duke CRADA approved. Enrollment has begun					
*Enrollment/data collection at VA; *HRPO approval/enrollment at WRNMMC					
Enrollment and data collection, initial analysis					
Clinical study closure, outcomes analysis, final adjudication					
<b>Estimated Budget (\$K)</b>		<b>\$389K</b>	<b>\$639K</b>	<b>\$692K</b>	<b>\$518K</b>

## Goals/Milestones

**CY13 Goal** – Protocol planning, data use agreements, IRB & HRPO approvals, lab supply purchasing and enrollment

☒ Fully planned, IRB approval at Duke & Durham VAMC, lab supplies purchased and lab analyses developed. CRADA between VA & Duke approved.

**CY14 Goals** – Patient enrollment, data and sample collection

☒ 1<sup>st</sup> patient enrolled 12/13 at Durham VAMC

☒ IRB approval & HRPO secondary approvals, Duke Enrollment

**CY15 Goal** – Patient enrollment, data collection, clinical adjudication

☒ Increased enrollment with 3<sup>rd</sup> study site, endpoint adjudications

**CY16 Goal** – Clinical study closure and outcomes analysis

☐ Final epigenetic analysis and endpoint adjudication

☐ Clinical outcomes analysis

## Comments/Challenges/Issues/Concerns

- There is now a third clinical site (Duke) and improved inclusion/exclusion criteria to avoid unnecessary patient exclusion

**Budget Expenditure to Date** (from start to date)

Projected Expenditure: \$1,720K

Actual Expenditure: \$1,153K

Updated: October 1, 2015